



COLOMBO PLAN



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The Center for Forensic
Science Research & Education

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Public safety and
public health
officials worldwide
should be aware of
an emerging threat
of diverted liquid
pharmaceutical
fentanyl, and other
liquid forms.

This threat could
have severe
implications for
the introduction
of fentanyl into a
country's illicit drug
supply, or make
an existing
fentanyl epidemic
worse.

EMERGING THREAT:

Injectable Liquid Fentanyl

- Fentanyl misuse or abuse typically involves injection or smoking of illicitly manufactured fentanyl (IMF). Illicit fentanyl is most commonly sold on the street as counterfeit tablets or as powders in folded glassine papers.
- Recently, however, diverted injectable solutions of pharmaceutical fentanyl have been reported in countries where IMF has not yet become established, such as Nigeria, Colombia and El Salvador (see details over); in addition to Argentina (500 vials), Brazil (72 vials), and Costa Rica (25 vials). Furthermore, there are reports of fentanyl injectable solutions being stolen or diverted from hospitals, clinics and medical supply houses in Panama (19,000 vials), the United States, and Europe.
- Pharmaceutical fentanyl citrate injection solution typically contains 50 micrograms of fentanyl citrate in each milliliter of solution (50 mcg/mL); a non lethal dose. However, injection of 5-10mL of these solutions can cause intoxication, and may lead to death in susceptible individuals or users without opioid tolerance.
- Diversion of pharmaceutical grade fentanyl in medicinal (non-lethal) doses has the potential to introduce fentanyl into local drug supplies in many countries that currently do not have a major illicit opioid problem, without attracting the attention of police and public health authorities following large overdose outbreaks.
- Not only can diverted medical fentanyl lead to opioid addiction, but when the source of diverted pharmaceutical fentanyl is shut off through interdiction or enforcement, local drug distributors and users may turn to the more dangerous powders and pills being produced by Mexican cartels to fill the demand, thereby increasing the risk of fatal overdose.
- IMF in powder and pill forms have been demonstrated to be difficult to produce consistently in non-lethal doses. The fentanyl content of these illicit pill and powder dosage forms has been shown to be highly variable which can lead to higher overdose death rates and lethal outbreaks.
- More recently, IMF in liquid (solution) form has also been seized in the United States in bulk quantities which are easier to conceal, transport and package for sale. These liquid solutions, however, can be as lethal as the standard powder and pill forms of the drug.
- Fentanyl can be recovered and concentrated in powder form from these IMF or diverted injectable solutions by chemical extraction or by evaporation, for example in a microwave, or the solutions can be directly injected. Recent U.S. seizures, however, indicate intent is for intravenous use in liquid form.
- Drug dealers may also mix adulterants (xylazine) and other drugs (e.g. cocaine, fentanyl analogs) into liquid fentanyl solutions creating complex lethal drug mixtures to mimic the effects of similarly adulterated fentanyl powders and pills.
- This health alert provides details of some of the liquid dosage forms that have been reported in international illicit drug markets. They may represent an emerging threat in countries that have not historically been exposed to illicit opioid use, or may exacerbate an existing IMF crisis like in the United States.

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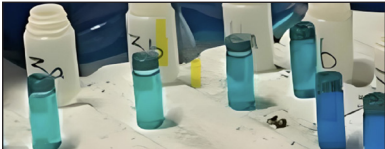

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International Reports of Injectable Liquid Fentanyl

COUNTRY	REPORTED ACTIVITY
<p>NIGERIA (May 2023)</p>	<ul style="list-style-type: none"> • NDLEA reported the seizure of diverted pharmaceutical am-poules of fentanyl in an open-air shopping market. Each ampoule contained 50 micrograms of fentanyl in 1 ml of so-lution. The initial source of the fentanyl was a pharmaceu-tical firm in the United Kingdom. • THREAT: These individual ampoules represent non-lethal doses that could introduce illicit fentanyl use in countries not previously exposed to this substance.
<p>COLOMBIA (2023)</p>	<ul style="list-style-type: none"> • Colombian National Police Antinarcotics teams intercepted shipments of medicinal fentanyl citrate in glass amber am-poules. The source of the fentanyl was a phar-maceutical manufacturer in Chile. Each ampoule contained 0.5 mg / 10 ml or 50 mcg / 1 ml of liquid fentanyl. Ampoules have been seized in Bogota, Medellin (280 vials), Tulua, and Cucuta. • THREAT: These individual ampoules represent non-lethal doses that could introduce illicit fentanyl use in countries not previously exposed to this substance.
<p>EL SALVADOR (May 2023)</p>	<ul style="list-style-type: none"> • El Salvador National Police seized 500 ampoules of medici-nal fentanyl citrate along their border with Honduras. The source of the fentanyl was a health agency in Guatema-la. Each ampoule contained 0.1 mg / 2 ml or 50 mcg / 1 ml of liquid fentanyl. • THREAT: These individual ampoules represent non-lethal doses that could introduce illicit fentanyl use in countries not previously exposed to this substance.



International Reports of Injectable Liquid Fentanyl

COUNTRY	REPORTED ACTIVITY
<p>HONDURAS (2023)</p>	<ul style="list-style-type: none"> In November, Honduran authorities seized 48,600 ampoules of medicinal-grade fentanyl packed into dozens of sealed cardboard boxes. The shipment originated in the UK. THREAT: These individual ampoules represent non-lethal doses that could introduce illicit fentanyl use in countries not previously exposed to this substance. 
<p>UNITED STATES (2023)</p>	<ul style="list-style-type: none"> In October & November 2023, large quantities of liquid injectable fentanyl solutions were seized in Arizona. The first seizure totaled 54 gallons, while the latter totaled 64 gallons. Intent was for intravenous use, to be further broken down into vials for individual sale and consumption. In July 2023, 1.58 kg of liquid fentanyl was seized in Kentucky. THREAT: Uniform individual doses of IMF liquid fentanyl would be extremely difficult to safely produce, resulting in similar risks for overdose as with traditional tablet or powder forms. <p>The DEA estimates that only 16g of fentanyl out of the 691kg U.S. 2022 fentanyl manufacturing quota was diverted from the medical supply. U.S. fentanyl nitrate injection solution typically contains 50 mcg / ml solution.</p> 
<p>EUROPE (May 2021)</p>	<ul style="list-style-type: none"> In 2021, European Union member states reported to the EMCDDA approximately 140 deaths associated with fentanyl. A significant portion of these, however, were thought to be associated with fentanyl diverted from medicinal use rather than fentanyl from illicit production. <p>https://www.emcdda.europa.eu/publications/European-drug-report/2023/drug-situation-in-europe-up-to-2023_en</p> 

International Reports of Injectable Liquid Fentanyl

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Questions? Please email Barry.Logan@cfsre.org.

PURPOSE

Selected samples seized from the United States Southwest border are submitted to the Center for Forensic Science Research and Education (CFSRE) for testing for research purposes of qualitative and quantitative testing. The purpose of this report is provide information on an atypical batch of counterfeit tablets that was received and tested which contained multiple complex drug mixtures representing a significant health threat.

BACKGROUND

Seized tablets and powders suspected of containing fentanyl are analyzed at CFSRE using a workflow that includes microscopic imaging of tablets using the MiScope® Megapixel MP3, qualitative analysis by both gas chromatography mass spectrometry (GC/MS) as well as liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) for identification of novel substances, and quantitative analysis using Waters® Acquity UPLC coupled with a Waters Xevo® TQ-S micro.

Images of Six Different Counterfeit Tablets in a Single Atypical Case



Figure 1. The tablets pictured were differentiated from each other based on differing colors and/or monogramming. The “30” marking on Exhibits 4 and 5 appear to be similar, but were differentiated based on color comparison and diagonal of M square measurement, which for Exhibit 4 was 4.95 mm and for Exhibit 5 was 5.85 mm. Exhibits 5 and 6 differed in the height of “0” measurement for the “30” monogram portion of the tablet. The height of zero measurement for Exhibit 5 was 1.50 mm and for Exhibit 6 was 2.21 mm. Exhibit 3 differed from the other exhibits because it appeared degraded and the monogramming could not be visually compared to the rest of the exhibits.

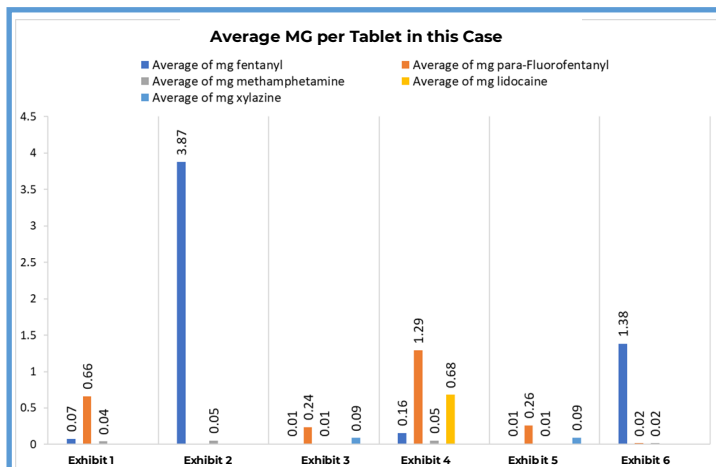
Combined Qualitative GC/MS and LC-QTOF-MS Results for All Exhibits Tested

	Fentanyl	Metamizole	Para-fluoro fentanyl	Acetaminophen	Methamphetamine	Fluoro phenethyl 4-ANPP	Despropionyl para-fluorofentanyl	4-ANPP	Xylazine	Pentobarbital	Levamisole	Lidocaine
Exhibit 1	X	X	X		X	X	X					
Exhibit 2	X	X		X	X			X				
Exhibit 3	X	X	X	X		X	X		X	X		
Exhibit 4	X	X	X	X	X	X	X				X	X
Exhibit 5	X	X	X	X	X	X	X					
Exhibit 6	X	X	X	X				X	X	X		

CFSRE received a case involving suspected counterfeit tablets seized at the US Southwest Border. It consisted of six separate exhibits containing a total of 40 counterfeit tablets. One tablet was tested from Exhibits 1-3, ten tablets were tested from Exhibit 4, twelve tablets were tested from Exhibit 5, and fifteen tablets were tested from Exhibit 6.

All 40 tablets contained fentanyl and the banned analgesic metamizole. The fentanyl analog para-fluorofentanyl was present in 5 of the exhibits. Other substances present in the tablets were the psychoactive substances methamphetamine, xylazine (a veterinary sedative) and pentobarbital (a veterinary euthanasia agent). The samples also contained other adulterants including acetaminophen, lidocaine the banned anti-worming agent levamisole, and chemical reaction by-products and precursors from illicit fentanyl manufacture.

NOTE: Although 2 mg is frequently considered a lethal fentanyl dose even in tolerant individuals, and the majority of cases analyzed contained less than 2 mg of fentanyl, almost all of these cases can still be considered potentially lethal due to the toxic and synergistic effects of adulterants such as para-fluorofentanyl, metamizole, xylazine, levamisole, methamphetamine, and pentobarbital. Much lower doses of fentanyl can also be lethal in individuals with less tolerance.



Ex	GC/MS Findings
1	Fentanyl , para-Fluorofentanyl , Methamphetamine , Metamizole Despropionyl para-fluorofentanyl, para-Fluorophenethyl 4-ANPP
2	Fentanyl , Methamphetamine Acetaminophen, Metamizole 4-ANPP
3	Fentanyl , para-Fluorofentanyl , Pentobarbital Acetaminophen, Metamizole Despropionyl para-fluorofentanyl, para-Fluorophenethyl 4-ANPP
4	Fentanyl , para-Fluorofentanyl , Methamphetamine Acetaminophen, Metamizole , Lidocaine , Levamisole 4-ANPP, Despropionyl para-fluorofentanyl, para-Fluorophenethyl 4-ANPP
5	Fentanyl , para-Fluorofentanyl , Methamphetamine , Pentobarbital Acetaminophen, Metamizole , Xylazine Despropionyl para-fluorofentanyl, para-Fluorophenethyl 4-ANPP
6	Fentanyl , para-Fluorofentanyl Acetaminophen, Metamizole 4-ANPP

A total of 40 tablets were quantitatively tested for all six exhibits. The average mg of para-fluorofentanyl was greater than the average mg of fentanyl for 4 out of the 6 exhibits (exhibits 1, 3, 4, and 5). The average mg of acetaminophen per tablet was greater than 60% for exhibits 2-5.

Fentanyl and metamizole were detected in every exhibit to a greater or lesser extent. In exhibits 1,3,4 and 5 however, the analog para-fluorofentanyl was the predominant opioid. Cutting agents highlighted in yellow can make the individual pills more potent and lethal.

Information Regarding Adulterants Effects on Human Health

Acetaminophen	An over the counter analgesic which is used to reduce pain and fever. Overdose can result in acute liver failure. Symptoms of a possible acetaminophen overdose also includes loss of appetite, nausea, vomiting, extreme tiredness, sweating, unusual bleeding or bruising, yellowing of skin or eyes, and pain in the abdomen (especially in the upper right side). Acetaminophen was detected in 5 out of the 6 exhibits.
Levamisole	A de-worming drug that is used for veterinary practice. It is most commonly used as a cutting agent in cocaine to modify the stimulant effects of the drug. Adverse effects of levamisole use include unexplained fever and agranulocytosis (lowering of white blood cells), unexplained vasculitis (damage to blood vessels) with purple skin lesions over ear lobes, legs and thighs, persistent or recurrent fever and chills, worsening or persistent sore throat, worsening swollen glands. Levamisole may also increase the toxic effects of opioids.
Lidocaine	A local anesthetic drug approved for human use, lidocaine is added to drug samples as a filler so that not as much actual drug product is added. Because it produces a numbing effect, like cocaine, lidocaine is added to minimize the discomfort that injection or snorting of drugs usually comes with. Lidocaine toxicity can manifest as cardiotoxicity which includes symptoms of abnormal heart rhythms, low blood pressure, or altered mental status. It can also manifest as methemoglobinemia for which symptoms include, cyanosis, low blood oxygen, distressed breathing, headache, dizziness, delirium, and seizures.
Metamizole	A non-opioid analgesic that is used in Europe, South America, and Asia today to combat pain, fever, and muscle spasms. It is also commonly known as dipyrone. Metamizole was removed from the medical drug market in the United States due to frequency of agranulocytosis. Other adverse effects include nausea, vomiting, abdominal pain, diarrhea, headache, dizziness, renal dysfunctions, and others. Less common effects are aplastic anemia and anaphylaxis. Metamizole may increase toxic effects of opioids and affect naloxone ability to reverse overdose
Pentobarbital	A barbiturate belonging to a class of sedative-hypnotic, seizure drugs which is widely used as a euthanasia agent in veterinary medicine. It has historically been used in humans as a medication used to treat or manage seizures, intracranial pressure control, and insomnia. Adverse effects of pentobarbital include altered mental status, agitation, confusion, drowsiness, respiratory depression, bradycardia, hypotension, cardiovascular collapse, dizziness, hallucinations, headache, insomnia, nausea, vomiting, hepatotoxicity. Symptoms of pentobarbital toxicity include airway compromise, cardiovascular collapse, coma, and death.
Xylazine	Xylazine is a veterinary sedative used in animal surgery and sedation. It has never been approved in the US for human use due to its adverse effects. It is one of the most common adulterants in fentanyl powders in the eastern and midwestern United States. Xylazine can be dangerous when taken in combination with illicit drugs. Its toxicity symptoms include CNS depression, sedation, respiratory depression, bradycardia, skin lesions, and slowed wound healing. While naloxone can reverse opioid effects it does not reverse the contribution to sedation from xylazine.

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